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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,693	10/16/2001	Jonathan S. Stamler	Duke 1931	3762

7590 06/01/2007

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ART UNIT	**PAPER NUMBER**
1636	

MAIL DATE	DELIVERY MODE
06/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/977,693	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-9 and 18-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27,28 and 30* is/are allowed.

6)☒ Claim(s) *1-3,5,6,8,9,18-22,25 and 26* is/are rejected.

7)☒ Claim(s) *7,23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 3/20/2007 in which claims 1-2, 5 and 8 were amended, claims 11-12 were cancelled, and claims 18-30 were added. Claims 1-3, 5-9 and 18-30 are pending and under examination in the instant Office action.

Any rejection of record not recited herein is hereby WITHDRAWN.

Claim Objections

Claims 6 and 28 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 5 is drawn to methods of correlating protein-protein interactions involved in one or more pathophysiological processes or one or more physiological processes with oxygen tension, comprising screening for protein-protein interactions between at least one protein and a plurality of proteins in the presence and absence of decreased oxygen tension from that in

room air, and then correlating the protein-protein interactions to identify at least one different protein-protein interaction wherein the at least one different protein-protein interaction is involved in one or more pathophysiological or physiological processes. Claim 6 is drawn to such a method wherein the at least one protein is "associated with a physiological process or a pathophysiological process" and as such does not further limit claim 5 because any protein involved in the identified protein-protein interaction of claim 5 would be "associated with a physiological or pathophysiological process."

Claim 27 is drawn to a method of correlating protein-protein interactions with oxygen tension comprising screening for protein-protein interactions between at least one protein and a plurality of proteins, wherein the screening is performed in the presence of decreased oxygen tension from that in room air and wherein the plurality of proteins are screen concurrently and further wherein a plurality of determinations are made in step (b) with different oxygen tensions being employed in each determination. Claim 28 is drawn to such a method also wherein a plurality of determinations are made in said method step with different oxygen tensions being employed in each determination. As such, claim 28 fails to further limit claim 27.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 8 recites "[t]he method of Claim 5 where the oxygen tensions employed in step (b) range from 0.1 mm Hg to 145 mm Hg" in lines 1-2 (emphasis added). Claim 8 is vague and indefinite in that "the oxygen tensions" lack clear and positive antecedent basis. Does Applicant intend the method of claim 7 where the oxygen tensions employed in step (b) range from 0.1 mm Hg to 145 mm Hg, or does Applicant intend some other set of oxygen tensions?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 5-6 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Poellinger et al (US Patent Application Pub. US/2002/0048794 A1; of record). **This rejection is maintained for reasons of record.**

Poellinger et al teach a method of establishing a protein-protein interaction map comprising (a) screening for a protein-protein interaction between at least one protein and a plurality of proteins, where the screening is performed in the absence of a simulated redox state perturbation and where the plurality of proteins are screened concurrently; (b) screening for a protein-protein interaction between the at least one protein and a plurality of proteins, where the screening is performed in the presence of a simulated redox state perturbation and where the plurality of proteins are screened concurrently; and (c) generating the protein-protein interaction map by identifying at least one different protein-protein interaction between (a) and (b) (see entire document, especially paragraphs 138-140 and Figures 19 and 20). Specifically, Poellinger et al screen for

protein-protein interactions between the GAL4/HIF-1α fusion protein and VHL and ARNT under normoxic and hypoxic conditions. The Western blots showing co-immunoprecipitation results as in Figures 19 and 20 are the "interaction map" and a noted difference in protein-protein interactions between (a) and (b) is, e.g., a difference in HIF-1α's ability to bind to Arnt and VHL under normoxic and hypoxic conditions. Arnt/HIF-1α binding occur under hypoxic conditions, but not under normoxic conditions, whereas hypoxia appears to have little effect upon the ability of HIF-1α to bind to VHL. Furthermore, these results anticipate the recited claims because any difference in protein-protein interactions of wild-type proteins identified under normoxic and hypoxic conditions would be comparative for the pathophysiological process of cellular response to hypoxia.

Response to Arguments

Applicant argues that Poellinger et al do not teach the establishment of a protein-protein interaction map wherein the changed protein interaction is for the comparison of or involvement in one or more pathophysiological processes. Applicant further argues that the HIF-1α/VHL interaction did not change under normoxic or hypoxic conditions. Applicant also argues that the only protein-protein interaction which did

change under normoxic and hypoxic conditions was the interaction between HIF-1α and Arnt; however, Applicant asserts that the interaction between HIF-1α and Arnt "does not involve a pathophysiological process or a physiological process" (see page 8, 1st full paragraph of the Remarks filed 3/20/2007). Applicant further argues that Poellinger et al do not teach any circumstances under which HIF-1α would be available to bind to Arnt under normoxic conditions and therefore that "any differential HIF-1/Arnt interaction under normoxic as compared to hypoxic conditions cannot involve a pathophysiological process or a physiological process" (ibid).

Applicant's arguments have been carefully considered and have respectfully been found unpersuasive. As explained above, Poellinger et al do in fact teach the establishment of a protein-protein interaction map wherein the changed protein interaction is for the comparison of or involvement in one or more pathophysiological process, i.e. hypoxia. Examiner agrees with Applicant insofar as only the HIF-1α/Arnt interactions were different under normoxic as compared to hypoxic conditions. However, only one different protein-protein interaction need be identified in order to anticipate the rejected claims. Furthermore, Applicant's assertion that Poellinger et al do not teach any circumstances under which HIF-1α would be available to

bind to Arnt under normoxic conditions and therefore that any differential HIF-1/Arnt interaction under normoxic as compared to hypoxic conditions cannot involve a pathophysiological process or a physiological process is not persuasive precisely because HIF-1α translocation is a consequence of the pathophysiological process (hypoxia) and therefore the difference in protein-protein interactions is "involved in" one or more pathological and/or physiological processes. The claims do not recite a limitation wherein the proteins involved in the protein-protein interaction remain available for binding in the presence of the simulated redox state perturbation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 18-20 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al (*Biochemical and Biophysical Research Communications* **275**:764-767, 2000) in view

of Klein et al (US Statutory Invention Registration H1892; IDS Ref AD). **This is a new rejection necessitated by Applicant's amendment.**

Applicant's invention is drawn to a method of identifying (establishing a map of) one or more protein-protein interactions comprising: (1) screening for protein-protein interactions between at least one protein and a plurality of proteins, wherein the screening is performed in the absence and in the presence of a simulated redox state perturbation and wherein the plurality of proteins are screened concurrently; (2) generating a protein-protein interaction "map" by identifying at least one different protein-protein interaction between those screened in the presence of a simulated redox state perturbation and those in the absence of a simulated redox state perturbation. The protein-protein interaction must be involved in one or more pathological or physiological processes. In one embodiment, Applicant's invention is drawn to a yeast two-hybrid method employed to generate a map of differences between protein-protein interactions in the presence and absence of a redox state modifier molecule such as hydrogen peroxide.

Martin et al teach a method wherein differences in protein-protein interactions are mapped as a function of oxidative stress. Specifically, Martin et al teach a method of

identifying differences in p16/Cdk4 interaction using a yeast two-hybrid assay. Yeast cells expressing GAL4-DBD-Cdk4 fusions or GAL4-AD-p16 fusions were cultured with and without hydrogen peroxide (a redox state modifier molecule) and inhibition of p16/Cdk4 binding was observed when the yeast cells were exposed to hydrogen peroxide (see entire document, especially page 766, Figure 1). Martin et al teach that Cdk4 is bound by p16 to prevent the cell from exiting the G1 phase of the cell cycle (see page 765, 1st full paragraph), thus the protein-protein interaction is "involved" in one or more pathological or physiological processes. The protein-protein interaction "map" generated by Martin et al is taught the form of Figure 1 (page 766) wherein the differences in p16/Cdk4 binding in the presence and absence of H_2O_2 is exemplified. Martin et al teach that the yeast two-hybrid system may be a good tool for investigating the mechanism by which oxidative stress can influence the interaction between proteins (see page 767, last paragraph). Martin et al do not teach such a method wherein protein-protein interactions between at least one protein and a plurality of proteins are screened concurrently in the presence and absence of a simulated redox state perturbation.

Klein et al teach that the yeast two-hybrid system is an "extremely useful" method for studying protein-protein

interactions (see entire document, especially column 4, lines 20-22). Klein et al further teach that the yeast two hybrid system offers a number of advantages for investigating protein interactions, including increased sensitivity as compared to co-immunoprecipitation, assessment of protein-protein interactions under conditions similar to those in which such interactions normally take place, and its usefulness in methods of high volume screening for specific inhibitors of protein-protein interactions (see column 5, lines 11-30). Klein et al teach that one embodiment of their invention comprises a process for "identifying many different interactions between protein pairs at once" which Klein et al refer to as a "multiple target approach" or "MTS" (see column 12, lines 2-9). One approach for the MTS strategy taught by Klein et al is to test multiple protein-protein interactions in the presence and absence of a compound and a molecule (pro-toxin) which, upon protein-protein binding inhibition, results in yeast cell growth because the pro-toxin would not be converted into toxin. This method, exemplified in Figure 2, would allow for easy identification of protein-protein interaction inhibitors.

It would have been obvious for one of ordinary skill in the art to combine the methods of Martin et al and Klein et al

because both references a drawn to the use of yeast two-hybrid assays to determine differences in protein-protein interactions.

One of ordinary skill in the art would have been motivated to combine the teachings of Martin et al and Klein et al because Martin et al suggest that the yeast two-hybrid assay is a "good tool" for investigating mechanisms by which oxidative stress can influence the interaction between proteins, and Klein et al teach that among the advantages of the two-hybrid system is its usefulness in methods of high volume screening for specific inhibitors of protein-protein interactions and for its ability to identify many different interactions between protein pairs at once.

One of ordinary skill in the art would have had a reasonable expectation of success because the yeast two-hybrid system was a well-documented system at the time of Applicant's filing and because Klein et al teach that such a system could be used to screen any number of compounds capable of inhibiting protein-protein interactions.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Martin et al with those of Klein et al.

Claims 1-3, 18-22 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al (*Biochemical and Biophysical Research Communications* **275**:764-767, 2000) in view of Klein et al (US Statutory Invention Registration H1892; IDS Ref AD) as applied to claims 1-3, 18-20 and 25-26 above, and further in view of Bradfield et al (WO 99/28464).

As explained above, Martin et al in view Klein et al teach a method wherein differences in multiple protein-protein interactions are mapped as a function of oxidative stress. Specifically, Martin et al teach a method of identifying differences in p16/Cdk4 interaction using a yeast two-hybrid assay wherein yeast cells expressing GAL4-DBD-Cdk4 fusions and/or GAL4-AD-p16 fusions were cultured with and without hydrogen peroxide (a redox state modifier molecule) (see entire document, especially page 766, Figure 1). Martin et al teach that Cdk4 is bound by p16 to prevent the cell from exiting the G1 phase of the cell cycle (see page 765, 1st full paragraph), thus the protein-protein interaction is "involved" in one or more pathological or physiological processes. The protein-protein interaction "map" generated by Martin et al is taught in the form of Figure 1 (page 766) wherein the differences in p16/Cdk4 binding in the presence and absence of H_2O_2 is

exemplified. Klein et al teach that the yeast two-hybrid system is an "extremely useful" method for studying protein-protein interactions, especially for high volume screening for specific inhibitors of protein-protein interactions among multiple protein pairs at once (see entire document, especially column 4, lines 20-22;column 5, lines 11-30; and column 12, lines 2-9). Finally, Martin et al teach that the yeast two-hybrid system may be a good tool for investigating the mechanism by which oxidative stress can influence the interaction between proteins (see page 767, last paragraph). Martin et al in view of Klein et al do not teach such a method wherein the oxidative stress is hypoxia.

Bradfield et al teach new and distinct members of the bHLH-PAS superfamily of transcription factors called "MOPS" or "members of PAS" as well as genetically engineered cells such as yeast cells or mammalian cells produced to express any one, or a combination of MOPS proteins (see entire document, including the Abstract and page 27, lines 14-37). Bradfield et al further teach that such cells can be used to study the effect of external stimuli (including oxidative stresses such as hypoxia (low oxygen tension) and cobalt chloride) on activation of MOPS proteins or MOPS signal transduction pathways (ibid and page 28, lines 10-20). Bradfield et al teach that in a preferred

embodiment a yeast two hybrid system is used to assess binding interactions between MOPS and other bHLH-PAS proteins, i.e. proteins involved in a physiological process.

It would have been obvious for one of ordinary skill in the art to combine the methods of Martin et al in view of Klein et al as applied to claims 1-3, 18-20 and 25-26 above, and further in view of Bradfield et al because all three references teach the use of yeast two-hybrid assays to assess protein-protein interactions and specifically methods of using such assays to determine the effects of compounds or stimuli to disrupt protein-protein interactions.

One of ordinary skill in the art would have been motivated to combine the method as taught by Martin et al in view of Klein et al with that of Bradfield et al because Martin et al teach that the yeast two-hybrid system may be a "good tool" for studying the effect of oxidative stress on physiologically relevant protein-protein interactions, and Bradfield et al teach the use of oxidative stresses such as hypoxia (low oxygen tensions) and cobalt chloride to map changes in protein-protein binding.

One of ordinary skill in the art would have had a reasonable expectation of success because the yeast two-hybrid system was a well-documented system at the time of Applicant's

filing and because Klein et al teach that such a system could be used to screen any number of compounds/stimuli capable of inhibiting protein-protein interactions.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Martin et al and Klein et al with those of Bradfield et al.

Allowable Subject Matter

Claims 27-28 and 30 are allowed.

Claims 7 and 23-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Joseph Woitach can be reached at (571) 272-0739.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

May 21, 2007

DAVID GUZO
PRIMARY EXAMINER